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AN INVESTIGATION ON THE OCCURRENCE
OF THE CHOLERA VIBRIO IN THE
BILIARY PASSAGES

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BY

MAJOR E. D. W. GREIG, M.D., D.S.C., I.M.S

On special duty for the Cholera Enquiry



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[MSS. received October 29, 1912. Read November 13, 1912.*]

INTRODUCTORY.

IN my researches¹ on the etiology of enteric fever in India, I dealt with the relation of the *b. typhosus* to the biliary passages and the important bearing which this had on the "carrier" question. When I was placed on special duty this year for the Cholera Enquiry of the Indian Research Fund Association, a problem which naturally presented itself was, is the cholera vibrio present in or absent from the biliary passages? Turning in the first place to the most recent monograph² on cholera in India (Rogers, 1911), for information on this point, I read, on page 65, the following sentence in this connection. "The absence of infection of the gall-bladder and bile ducts by the comma bacillus places the disease in quite a different position from that of typhoid in this respect."

Early observations on the cholera vibrio in bile.—On referring to the literature I find that some observations had been made, before the important relationship of the occurrence to the epidemiology of cholera was appreciated. Thus Nicati and Rietsch (1884)³ examined the bile in 3 cases of cholera and found the vibrio in two. On another occasion

* At All-India Sanitary Conference, Madras.

they examined 5 cholera cases and found the vibrio in the bile in 2. Similar observations were made by Doyen (1884)⁴, Tizzoni and Cantani (1886)⁵, J. F. Rapschevsky (1886)⁶, L. P. Rekovsky (1882)⁷.

Kulescha⁸ examined recently 109 cholera cases and found the cholera vibrio in the gall-bladder in 49, and in 10 per cent. of the cases he observed changes in the biliary passages.

L. Brulloff⁹ has found the cholera vibrio in the bile *post-mortem* very frequently, in 76 per cent. of the cases examined, and also in the blood and other organs. C. Defressine and H. Cazeneuve¹⁰ in November 1911, in a small epidemic of cholera at Toulon, found cholera vibrios in the bile in 3 cases.

The "carrier" question is one of vital concern in regard to the prevention of cholera and an elucidation of the exact mode of production of the "cholera carrier" is, therefore, a problem of fundamental importance.

This year being the "Nutan Kalebar" Festival of Jagannath an unusually large number of pilgrims, about 300,000, visited Puri during the Car-pulling. As a result of this the annual number of cholera cases was greatly increased, and I had a very large amount of valuable material for the purpose of my research. I was enabled to systematically investigate the relationship of the cholera vibrio to the biliary passages. I had an opportunity of making a bacteriological examination of the bile in 271 fatal cases; and the result of this investigation showed that the cholera vibrio was found in no less than 80; and that distinct pathological changes, both naked eye and microscopic, were found in the gall-bladder in 12 of these 80 cases. Further it is interesting to note that the comma bacillus is found, on section of the gall-bladder, to be present not only on the surface of the mucous membrane but, also, deeper in the sub-mucous tissue. So far as I am aware my series of observations on the occurrence of the cholera vibrio in the biliary passages is the largest recorded in the literature.

Before proceeding to describe my research in detail, it may be well to direct attention to the importance of this observation in relation to the causation and prevention of cholera.

If the cholera vibrio is an inhabitant of the intestine only and does not gain access to the biliary passages as stated¹¹ in a standard textbook of bacteriology, a view which is very generally held at present

then the conditions for the prolonged life of the organism in the body of the host after recovery from the acute attack would be much less favourable, as the delicate comma bacillus would have to enter into a struggle with the other intestinal and putrefactive organisms, and that too in an unfavourable medium. Although an "acute or temporary carrier" might result the possibility of a "permanent chronic cholera carrier" being produced in these circumstances would be slight. On the other hand, if it can enter the gall-bladder it finds there ideal conditions for its prolonged life, namely, the absence of other competitors and a suitable alkaline medium, indeed Ottolenghi¹² has recently recommended bile as a selective medium for "enriching" the comma bacillus in place of peptone water, and I can confirm the value of this medium from my experience. My researches have demonstrated that the cholera vibrio can enter and live in the bile, and the fact that it does so increases the chances of the production of the "chronic cholera carrier." From the point of view of the prevention of cholera the "chronic carrier" is a much more serious problem to deal with than an "acute carrier," although the latter is by no means without significance and both deserve close consideration. An apparently healthy person, whether convalescent or "contact" harbouring the cholera vibrio in the gall-bladder, is dangerous in a high degree, because he is liable to start fresh foci of infection, it may be in various widely separated places to which he may travel, and, possibly, retain in his body the organism of cholera for prolonged periods. Such a person acts as a reservoir of the virus.

Owing to the fact that the recovery from cholera is remarkably fast and that the patients are, as a rule, discharged at the first opportunity from hospital, there is much greater danger in this disease of highly infective persons returning to the community than in enteric fever, in which the convalescence is slower. In another communication I shall deal with the question of cholera convalescents.

Methods.

As soon as possible after the death of the cholera patient I removed the gall-bladder having previously ligatured the common bile duct. The gall-bladders were sent to my temporary laboratory at Puri and the following technique for their investigation was adopted. A

small part of the outside of the gall-bladder was seared with a hot glass rod, and through this sterile patch a sterile glass pipette was passed and the bile drawn up and transferred to suitable media. After this operation the gall-bladder was opened and the condition of its wall and contents noted: if there was any sign of pathological alteration in the wall a portion was taken, fixed and hardened for sectioning in paraffin. For the bacteriological investigation I used at first, (*a*) ordinary agar slopes, (*b*) agar plates with preliminary "enrichment" in peptone water, (*c*) plating on Dieudonné medium; as the observations went on I found that equally good results were obtained by the first method (*a*), *i.e.*, transference of a small quantity of bile to agar slopes with a sterile pipette, as with the other two methods, so that latterly I confined myself to method (*a*) only. The culture was in each case tested with a high titre cholera agglutinating serum, one prepared by myself by treating rabbits intravenously with increasing doses of a living agar culture of a cholera vibrio obtained from a fatal case in Calcutta. The titre of my serum was 1—8,000. I also used as a control a high titre cholera agglutinating serum (1—10,000) obtained from the Swiss Serum and Vaccine Institute, Berne, prepared under the supervision of Professor Kolle. With a low dilution of these sera (1—50) immediate clumping, observed microscopically, occurred when the cholera vibrio culture was mixed with a small quantity of the serum dilution on a slide, and when tested subsequently the vibrios agglutinated to the end point of the high titre serum. Each culture was examined also microscopically, both stained and unstained, to determine whether or not the organisms had the characters of the cholera vibrio. The appearance on various other culture media was noted also. The identity of each strain was thus fully established by microscopic, cultural, and serological tests.

Tissue for examination was fixed in alcohol and prepared and embedded in paraffin in the usual manner. Serial sections were cut and stained in carbol fuchsin and in carbol thionine. Drawings were prepared to show the details of the structural changes.

RECORD OF OBSERVATIONS.

The following table shows the sex, the date of death, the condition of the bile and the gall-bladder, and the presence or absence of the cholera vibrio in the bile of fatal cases of cholera. In all except one

case the gall-bladder was examined on the same day as that on which the death took place. All were Hindu pilgrims:—

No.	Sex.	Date of death.	Condition of the bile and the gall-bladder.	Presence or absence of cholera vibrio in bile.
1	F.	20th July 1912	Dark ; normal	+
2	M.	Ditto	Yellow ; normal	+
3	F.	Ditto	Dark ; normal	— (Sterile).
4	F.	Ditto	Ditto	— Do.
5	F.	Ditto	Ditto	— Do.
6	F.	Ditto	Yellow ; normal	— Do.
7	M.	Ditto	Dark ; normal	— Do.
8	M.	21st July 1912	Dark, fluid ; normal	— Do.
9	M.	Ditto	Dark green, viscid, large gall stones	+
10	F.	Ditto	Dark green ; healthy	— Do.
11	F.	Ditto	Ditto	+
12	M.	Ditto	Dark brown, fluid ; bile stained	+
13	F.	Ditto	Dark fluid ; healthy	+
14	M.	Ditto	Dark viscid ; healthy	— (Other col.)
15	M.	Ditto	Light green fluid ; healthy	— Do.
16	M.	Ditto	Yellow fluid ; healthy	+
17	F.	Ditto	Dark viscid ; healthy	+
18	M.	Ditto	Ditto	— (Sterile).
19	M.	Ditto	Ditto	— Do.
20	M.	Ditto	Dark brown ; healthy	— Do.
21	M.	Ditto	Dark green fluid ; normal	— Do.
22	F.	Ditto	Dark viscid ; normal	— Do.
23	M.	Ditto	Dark fluid ; normal	+
24	F.	Ditto	Dark brown : normal, pigmented	+
25	M.	Ditto	Dark tarry ; normal	— (Other col.)
26	F.	Ditto	Ditto	— (Sterile).
27	M.	Ditto	Dark brown ; normal	— Do.
28	F.	Ditto	Dark ; normal ; pigmented	— Do.
29	M.	22nd July 1912	Dark fluid ; healthy	— Do.
30	F.	Ditto	Very dark fluid ; healthy	— Do.
31	M.	Ditto	Thick dark ; healthy, pigmented	— Do.
32	F.	Ditto	Dark tarry ; healthy	— Do.
33	M.	Ditto	Ditto	— Do.
34	M.	Ditto	Dark green viscid ; healthy, pigmented	— Do.
35	F.	Ditto	Dark green fluid ; healthy	+
36	F.	Ditto	Ditto	— Do.
37	M.	Ditto	Very dark tarry ; healthy	— Do.
38	M.	Ditto	Ditto	+
39	F.	Ditto	Dark fluid ; healthy	— Do.
40	M.	Ditto	Ditto	— Do.
41	F.	Ditto	Dark brown fluid ; healthy	— Do.
42	M.	Ditto	Dark tarry ; healthy	+
43	F.	Ditto	Ditto	— Do.
44	M.	Ditto	Dark fluid ; healthy	— Do.
45	F.	Ditto	Fluid ; healthy	— Do.
46	M.	Ditto	Dark tarry ; healthy	+
47	F.	Ditto	Fluid dark ; healthy	— Do.
48	M.	Ditto	Dark viscid ; healthy, pigmented	— Do.
49	F.	Ditto	Tarry bile ; healthy	— Do.
50	M.	23rd July 1912	Dark green fluid bile ; thickened	— Do.
51	M.	Ditto	Dark tarry ; normal	— Do.
52	F.	Ditto	Ditto	+
53	M.	Ditto	Ditto	— Do.
54	F.	Ditto	Dark tarry ; healthy	— Do.
55	M.	Ditto	Dark brown ; healthy	— Do.
56	F.	Ditto	Dark tarry ; healthy	+

No.	Sex.	Date of death.	Condition of the bile and the gall-bladder.	Presence or absence of cholera vibrio in bile.
57	F.	23rd July 1912	... Very little bile ; shrunk and small	— (Sterile.)
58	M.	Ditto	... Dark tarry ; healthy ...	— Do.
59	F.	Ditto	... Ditto ...	— Do.
60	M.	Ditto	... Dark ; healthy ...	— Do.
61	F.	Ditto	... Dark brown ; healthy ...	— Do.
62	M.	Ditto	... Dark fluid ; healthy ...	+
63	M.	Ditto	... Dark green viscid ; healthy ...	— Do.
64	M.	Ditto	... Fluid green ; healthy ...	— Do.
65	M.	Ditto	... Dark fluid ; wall healthy ...	+
66	M.	24th July 1912	... Thick tarry ; healthy ...	+
67	M.	Ditto	... Dark green viscid ; healthy ...	+
68	M.	Ditto	... Tarry ; healthy ...	— Do.
69	M.	Ditto	... Yellowish green fluid ; healthy ...	— Do.
70	F.	Ditto	... Dark green fluid ; healthy ...	— Do.
71	F.	Ditto	... Dark fluid ; healthy ...	— Do.
72	F.	Ditto	... Dark brown viscid ; healthy ...	— Do.
73	M.	Ditto	... Dark brown ; healthy ...	— Do.
74	M.	Ditto	... Dark tarry ; healthy ...	+
75	M.	Ditto	... Dark fluid ; healthy ...	— Do.
76	M.	Ditto	... Green fluid ; healthy ...	+
77	M.	Ditto	... Enlarged $7 \times 2\frac{1}{2}$ thin (full of dark bile) healthy.	—
78	F.	Ditto	... Dark green fluid ; healthy ...	+
79	F.	Ditto	... Dark tarry ; healthy ...	+
80	F.	Ditto	... Dark fluid ; healthy ...	—
81	M.	Ditto	... Ditto ...	+
82	M.	Ditto	... Ditto ...	— Do.
83	M.	Ditto	... Clear yellowish slightly fluid ; congested.	— Do.
84	M.	Ditto	... Dark fluid ; healthy ...	— Do.
85	M.	Ditto	... Ditto ...	+
86	M.	Ditto	... Small contracted ; wall congested and adherent to liver somewhat thickened ; contains light brown fluid.	— Do.
87	F.	25th July 1912	... Dark tarry ; healthy ...	— Do.
88	F.	Ditto	... Dark fluid ; healthy ...	+
89	F.	Ditto	... Ditto ...	— Do.
90	F.	Ditto	... Dark tarry ; healthy ...	+
91	M.	Ditto	... Ditto ...	— Do.
92	M.	Ditto	... Thick tarry ; healthy ...	— Do.
93	M.	Ditto	... Distended with light brown bile healthy.	— Do.
94	M.	Ditto	... Dark green fluid ; healthy ...	— Do.
95	M.	Ditto	... Light brown fluid ; three gall-stones.	— Do.
96	M.	Ditto	... Thick tarry ; healthy ...	— Do.
97	M.	Ditto	... Green tarry ; healthy ...	+
98	M.	Ditto	... Dark tarry ; healthy ...	— Do.
99	M.	Ditto	... Ditto ...	— Do.
100	F.	Ditto	... Filled up with two large gall-stones ; bile escaped in removing it.	— Do.
101	F.	Ditto	... Green fluid ; healthy ...	+
102	F.	Ditto	... Thin fluid bile ; healthy ...	+
103	M.	Ditto	... Dark tarry ; healthy ...	— Do.
104	M.	Ditto	... Dark brown ; healthy ...	+
105	M.	Ditto	... Dark tarry ; healthy ...	— Do.
106	M.	Ditto	... Ditto ...	— Do.
107	M.	Ditto	... Dark brown ; healthy ...	— Do.
108	M.	Ditto	... Very thick tarry ; healthy ...	— Do.
109	M.	26th July 1912	... Dark green ; healthy ...	— Do.

No.	Sex.	Date of death.	Condition of the bile and the gall-bladder.	Presence or absence of cholera vibrio in bile.
110	M.	26th July 1912	Dark fluid ; healthy ...	+
111	F.	Ditto	Dark brown ; healthy ...	— (Sterile.)
112	F.	Ditto	Dark tarry ; healthy ...	+
113	F.	Ditto	Ditto ...	— Do.
114	M.	Ditto	Yellow ; wall intensely congested throughout.	+
115	M.	Ditto	Dark tarry ; wall healthy ...	— Do.
116	M.	Ditto	Ditto ...	+
117	M.	Ditto	Ditto ...	— Do.
118	F.	Ditto	Yellow green ; wall congested in patches.	+
119	F.	Ditto	Tarry black ; wall healthy ...	— Do.
120	F.	Ditto	Ditto ...	+
121	F.	27th July 1912	Yellow ; healthy ...	— Do.
122	F.	Ditto	Dark tarry ; healthy ...	+
123	F.	Ditto	Ditto ...	— Do.
124	F.	Ditto	Brown liquid ; healthy ...	— Do.
125	F.	Ditto	Brown viscid ; healthy ...	— Do.
126	M.	Ditto	Ditto ...	+
127	M.	Ditto	Dark tarry ; healthy ...	— Do.
128	M.	Ditto	Dark green ; healthy ...	— Do.
129	M.	Ditto	Brown fluid ; healthy ...	— Do.
130	M.	Ditto	Dark tarry ; healthy ...	— Do.
131	M.	Ditto	Ditto ...	— (Other col.)
132	M.	Ditto	Dark brown ; healthy ...	— (Sterile.)
133	F.	Ditto	Dark tarry ; healthy ...	+
134	F.	Ditto	Dark brown ; healthy ...	+
135	F.	Ditto	Dark tarry ; healthy ...	— (Sterile.)
136	M.	28th July 1912	Ditto ...	— Do.
137	M.	Ditto	Dark brown, tarry ; healthy ...	— Do.
138	M.	Ditto	Dark tarry ; healthy ...	— Do.
139	M.	Ditto	Dark green tarry ; healthy ...	— Do.
140	M.	Ditto	Ditto ...	— Do.
141	F.	Ditto	Ditto ...	— Do.
142	M.	29th July 1912	Dark tarry ; healthy ...	— Do.
143	M.	Ditto	Ditto ...	— Do.
144	M.	Ditto	Ditto ...	— Do.
145	M.	Ditto	Ditto ...	+
146	M.	Ditto	Dark green ; healthy ...	— Do.
147	M.	Ditto	Dark tarry ; healthy ...	— Do.
148	M.	Ditto	Dark yellow ; healthy ...	— Do.
149	M.	Ditto	Dark brown ; healthy ...	+
150	F.	Ditto	Dark tarry ; healthy ...	+
151	F.	Ditto	Dark green ; healthy ...	+
152	F.	Ditto	Dark tarry ; healthy ...	+
153	F.	Ditto	Dark fluid ; healthy ...	— Do.
154	F.	Ditto	Yellow fluid ; inflamed ...	+
155	F.	Ditto	Dark tarry ; healthy ...	— (Other col.)
156	F.	Ditto	Very dark tarry ; healthy ...	— (Sterile.)
157	M.	Ditto	Dark tarry ; healthy ...	—
158	M.	Ditto	Ditto ...	—
159	M.	Ditto	Dark green ; healthy ...	—
160	M.	31st July 1912	Dark brown fluid ; wall greatly thickened and inflamed.	+
161	M.	Ditto	Pale green very fluid ; 2 gall stones ; wall healthy.	+
162	M.	Ditto	Dark tarry ; healthy ...	— (Other col.)
163	F.	Ditto	Ditto ...	—
164	M.	Ditto	Dark green fluid ; healthy ...	+ (Sterile.)
165	F.	Ditto	Dark tarry bile ; healthy ...	— Do.
166	M.	Ditto	Ditto ...	+
167	M.	Ditto	Ditto ...	— Do.

No.	Sex.	Date of death.	Condition of the bile and the gall-bladder.	Presence or absence of cholera vibrio in bile.
168	M.	31st July 1912	Yellowish fluid ; healthy	— (Other col.)
169	M.	1st August 1912	Brown fluid bile ; healthy	— Do.
170	M.	Ditto	Dark tarry ; healthy	— (Sterile.)
171	M.	Ditto	Ditto	+
172	M.	Ditto	Dark green fluid ; healthy	+
173	M.	Ditto	Viscid green bile ; healthy	+
174	F.	Ditto	Brown fluid ; congested	— Do.
175	M.	Ditto	Dark green viscid ; healthy	+
176	F.	2nd August 1912	Dark brown fluid ; healthy	+
177	F.	Ditto	Green fluid ; healthy	+
178	M.	Ditto	Dark tarry bile ; healthy	— Do.
179	F.	Ditto	Yellow viscid (somewhat) ; intensely congested	+
180	F.	3rd August 1912	Dark tarry ; healthy	+
181	M.	Ditto	Ditto	— Do.
182	M.	4th August 1912	Dark brown viscid ; healthy	— Do.
183	M.	Ditto	Dark tarry ; healthy	— Do.
184	M.	Ditto	Ditto	— Do.
185	M.	Ditto	Dark brown viscid ; healthy	+
186	F.	5th August 1912	Green fluid ; healthy	+
187	M.	Ditto	Brown fluid ; healthy	— Do.
188	M.	6th August 1912	Dark tarry ; healthy	— Do.
189	M.	Ditto	Dark fluid bile ; healthy	— Do.
190	F.	Ditto	Dark green bile ; congested	— Do.
191	F.	Ditto	Dark colour bile ; healthy	— Do.
192	M.	7th August 1912	Dark brown ; healthy	— Do.
193	M.	Ditto	Dark fluid ; healthy	— Do.
194	M.	Ditto	Tarry bile ; healthy	— Do.
195	M.	8th August 1912	Dark tarry bile ; healthy	— Do.
196	F.	9th August 1912	Fluid dark ; healthy	— Do.
197	F.	Ditto	Dark brown ; healthy	— Do.
198	M.	Ditto	Dark fluid ; healthy	— Do.
199	M.	Ditto	Ditto	— Do.
200	M.	Ditto	Ditto	— Do.
201	M.	Ditto	Ditto	+
202	M.	Ditto	Ditto	— (Other col.)
203	M.	Ditto	14 gall stone ; healthy	— (Sterile.)
204	M.	Ditto	Dark tarry ; healthy	— (Other col.)
205	M.	Ditto	Ditto	— (Sterile.)
206	F.	Ditto	Ditto	— Do.
207	M.	10th August 1912	Fluid bile ; healthy	— Do.
208	M.	Ditto	Dark tarry ; healthy	+
209	M.	Ditto	Fluid ; healthy	— Do.
210	M.	Ditto	Ditto	— Do.
211	M.	Ditto	Dark tarry ; healthy	— Do.
212	M.	11th August 1912	Dark green ; healthy	— (Other col.)
213	M.	Ditto	Ditto	— (Sterile.)
214	...	Ditto	Ditto	— Do.
215	...	Ditto	Ditto	— Do.
216	...	Ditto	Ditto	+
217	...	Ditto		+
218	F.	12th August 1912	Green fluid ; healthy	— Do.
219	F.	Ditto	Dark tarry ; healthy	+
220	F.	Ditto	Ditto	— Do.
221	M.	Ditto	Dark brown ; health	— Do.
222	F.	13th August 1912	Dark green fluid ; healthy	— Do.
223	F.	Ditto	Ditto	— (Other col.)
224	M.	Ditto	Ditto	+
225	M.	Ditto	Ditto	+
226	M.	Ditto	Ditto	— (Sterile.)
227	M.	Ditto	Dark tarry viscid ; healthy	— Do.
228	M.	15th August 1912	Dark fluid ; healthy	— Do.

No.	Sex.	Date of death.	Condition of the bile and the gall-bladder.	Presence or absence of cholera vibrio in bile.
229	M.	15th August 1912	Dark viscid ; healthy	— (Sterile.)
230	M.	Ditto	Ditto	— Do.
231	M.	Ditto	Dark viscid ; healthy	— Do.
232	M.	Ditto	Dark tarry ; healthy	— Do.
233	M.	Ditto	Dark brown ; slightly congested	+
234	M.	16th August 1912	Dark fluid ; healthy	— (Other col.)
235	M.	Ditto	Dark tarry ; healthy	— (Sterile.)
236	M.	Ditto	Ditto	— (Other col.)
237	M.	Ditto	Ditto	— Do.
238	M.	Ditto	Dark fluid brown ; healthy	— Do.
239	M.	Ditto	Dark tarry ; healthy	— Do.
240	M.	Ditto		— (Sterile.)
241	M.	Ditto		— Do.
242	M.	Ditto	Dark tarry ; healthy	— Do.
243	F.	17th August 1912	Ditto	— Do.
244	M.	Ditto	Dark green fluid ; healthy	— Do.
245	M.	Ditto	Dark tarry ; healthy	+
246	F.	18th August 1912	Ditto	— Do.
247	F.	Ditto	Yellowish brown ; healthy	— (Other col.)
248	M.	Ditto	Dark tarry ; healthy	— (Sterile.)
249	M.	19th August 1912	Fluid brown ; healthy	+
250	F.	Ditto	Green fluid ; healthy	— (Other col.)
251	M.	Ditto	Brown fluid ; congested	— Do.
252	M.	20th August 1912	Tarry ; healthy	— (Sterile.)
253	M.	Ditto	Ditto	— Do.
254	F.	Ditto	Dark green fluid ; congested	+
255	M.	21st August 1912	Liquid brown ; healthy	— (Other col.)
256	M.	Ditto	Dark tarry bile ; healthy	+
257	M.	Ditto	Dark fluid ; healthy	+
258	F.	Ditto	Dark brown ; healthy	— (Sterile.)
259	M.	Ditto	Ditto	— Do.
260	F.	Ditto	Ditto	— Do.
261	M.	Ditto	Ditto	+
262	F.	22nd August 1912	Dark green ; healthy	— Do.
263	M.	23rd August 1912	Ditto	+
264	F.	25th August 1912	Light green ; injected	+
265	M.	Ditto	Dark green fluid ; healthy	— Do.
266	F.	27th August 1912	Dark brown ; healthy	— (Other col.)
267	M.	28th August 1912	Dark tarry ; healthy	+
268	M.	30th August 1912	Yellowish brown ; healthy	— Do.
269	M.	Ditto	Intensely inflamed	+
270	M.	1st September 1912	Liquid greenish bile ; wall healthy	— (Sterile.)
271	F.	4th September 1912	Intensely inflamed	+

From these results it will be seen that the cholera vibrio can enter and develop in the bile. In the great majority of cases in which the comma bacillus was determined it was present in large numbers and in pure culture showing that it had found a particularly favourable medium for its growth. It is obvious that the bile containing the cholera vibrio in large numbers will be poured out into the small intestine and the organisms will gain an exit to the outside world with the faeces. I have determined the presence of the cholera vibrio in the stool of a person who was quite healthy at the time but had

passed through an attack of cholera some weeks previously. In examining a number of cholera convalescents daily I have noted¹³ that the discharge of the vibrios may be intermittent as in the case of *b. typhosus*. Zlaloroff⁴ has found the cholera vibrio in the stool one year after the attack.

These observations have a most important relation to the epidemiology of cholera because they afford a rational explanation in harmony with recorded facts of the mode of production of the "chronic carrier."

In 68 cases no pathological change was observed in the biliary passages although the comma bacillus was present in pure culture; like the *b. typhosus* the cholera vibrio can live in the biliary system without producing a pathological reaction, although, as we shall see, this is not invariably the case, and interesting pathological changes are found in the gall-bladder in some cases. In typhoid fever the *b. typhosus*, after circulating in the blood stream for a time, deposits locally in various tissues and appears to gain access to the biliary passages from the blood stream. In cholera it may be that the entrance is from the intestine, cholera vibrios being very abundant in the (rice water) contents of the small intestine, differing in this respect from the *b. typhosus*; the observations of Brulloff¹⁴, however, already referred to, who found the cholera vibrio in the blood, and, also, my own observation, that the comma bacillus may occur in the lung, dealt with later in this paper, have to be remembered; it may hereafter be shown that the cholera vibrio like the *b. typhosus* gains an entrance to the bile by the blood stream. Baroni V and Ceaparie Victoria¹⁵ injected large quantities of cholera vibrios into the ear vein of a rabbit and they found them in the bile 30 minutes after injection, but not in the small intestine till one hour after. In small doses the vibrios rapidly disappear from the circulation and deposit in the small intestine, appendix, and the bile. In the urine the vibrio was never found.*

It is interesting to note that the bile, from cases of cholera, in which the vibrio was not found, was, as a rule, sterile—163 out of a

* *Note*.—Since this paper was written I have determined the presence of the cholera organism in the urine of cholera cases. (See Preliminary Note on the occurrence of the comma bacillus in the urine of cholera cases. Greig, Indian Journal of Medical Research, Vol. I, p. 90, 1913).

total of 190 cases; of the remaining 27 cases in which the bile was found to contain other organisms a certain number may be accounted for by *post-mortem* invasion of the bile. The bile, being generally sterile, is, for this reason, a very suitable habitat for the delicate comma bacillus, as there are no other organisms to interfere with its growth, such as it would meet with in the intestine.

Pathological changes in the gall-bladder in cholera cases.—In my previous researches on enteric fever in India, 1906, I noted that the b. typhosus could give rise to cholecystitis. Forster¹⁶ of Strassburg was the first to associate gall-bladder complaints with the “carrier” in typhoid fever. Ledingham¹⁷, Droba (1899)¹⁸, Miller (1899)¹⁹, Brion (1910)²⁰, Findlay and Buchanan (1906)²¹, Simion (1907)²², Dudgeon (1908)²³, and other observers have recorded cases in connection with typhoid fever, but the relationship of the cholera vibrio to pathological lesions of the gall-bladder has received very little attention. Yet, both in view of the elucidation of the “carrier” question and the possible causal connection of gall-bladder infection with the various toxic sequelæ met with in cholera, the subject is one of great practical importance. I have already referred to the work of Kulescha²³ on the gall-bladder in cholera. He records an interesting case not recognised as cholera during life, but at the *post-mortem* examination the biliary passages in the liver were found to be greatly distended and filled with pus from which the cholera vibrio was isolated. Sections showed that there were other organisms present so that it could not be regarded as a pure vibrio infection.

During convalescence from cholera I have observed in a few cases that pain has been complained of in the right hypochondrium; and on palpation a tender swelling, having the shape and position of the gall-bladder, has been felt. This swelling subsided in a few days in each case and the patients recovered.

In a case recorded by me²⁴ in which the patient lived for 12 days after recovery from the acute attack of cholera and finally died of uræmia, the gall-bladder was found to be intensely congested and the bile contained a pure culture of the comma bacillus. It is possible that the common fatal complication of cholera, uræmia, is brought about, in certain cases at least, by the continuance of an active focus of infection in the gall-bladder, toxins being absorbed from it into the general

circulation and giving rise to lesions of the kidneys and other organs.

A point of special interest in the case above referred to was that patches of consolidation were present in the right lung and that smear preparations and sections made from these areas showed the presence of a comma bacillus, which must have gained access to the lungs by the blood stream, and the question arises therefore whether or not cholera is to be regarded as a septicæmia rather than a pure toxæmia.* Including this case I found distinct pathological changes in the gall-bladder in 12 cases in my series in which the cholera vibrio was present in pure culture in the bile.

Since recording the above case I have had an opportunity of studying in detail another case of cholera in which the gall-bladder showed marked pathological changes and the bile contained a pure culture of the cholera vibrio. It may be well to give a short history of this case here :—

Name.—Champa, Hindu, female, age 55, admitted on 4th September 1912, at 1-30 P.M. Died 9 P.M.

State on admission.—Patient was brought to hospital in an unconscious condition. She had been attacked 3 days previously. Stools typical (rice water), vomiting and purging. Pulse imperceptible. She was injected intravenously immediately after arrival with 4 pints of hypertonic salt solution. The pulse became perceptible after transfusion. Permanganate was given by the mouth. At about 5 P.M. the pulse again became imperceptible and another intravenous injection of hypertonic salt solution was given, but the pulse did not improve. Rectal injections of normal salines were given every 2 hours.

Post-Mortem Examination.—5th September 1912.

External appearance.—Body fairly well nourished.

No increase of fluid in pleural or pericardial cavities.

Right Lung.—Weight 12 oz. Somewhat congested, especially the lower lobe, otherwise no noteworthy change.

Left Lung.—Weight 12 oz. No noteworthy change.

* *Note.*—The occurrence of the comma bacillus in the urine supports the view that in a certain number of cases at least, cholera is a septicæmia. (See Preliminary Note on the occurrence of the comma bacillus in the urine of cases of cholera, Greig. Indian Journal of Medical Research, Vol. I, 1913).

Heart.—Weight 6 oz. There is some hypertrophy of the wall of the left ventricle, otherwise no noteworthy change.

No increase of peritoneal fluid.

Liver.—Weight 2 lb. 2 oz. It is congested and somewhat friable.

Gall-bladder.—It is very small and shrunken; it was removed after ligation of the duct and a portion of the surface was seared with a hot rod, and a pipette passed through the wall at the seared patch and some of the contents drawn off and inoculated on an agar slope. Next day this was found to contain a pure growth of cholera vibrio. On opening the gall-bladder there was a small quantity of dirty brown coloured bile. The mucous membrane was intensely congested and showed areas of hæmorrhage in the submucosa.

Right Kidney.—Weight 4 oz. Capsule is distinctly adherent and the substance tears on stripping it. Surface has a mottled pale grey appearance.

On section.—The cortex is pale grey with red points; pyramids pale red in colour.

Left Kidney.—Weight 5 oz. General condition practically the same as the right.

Spleen.—Normal.

Stomach and intestines.—Contents of small intestine watery.

Remarks.—In this case, also, the gall-bladder showed marked pathological change and the bile contained a pure culture of the cholera vibrio. The patient was a female of 55 years of age and the kidney showed the appearances of a lesion of old standing and the heart showed some hypertrophy of the wall of the left ventricle. The toxins of cholera absorbed both from the intestine and gall-bladder acted on the already damaged organs with the result that the first rally was followed by a second and fatal collapse. The patient died on the fourth day after the attack. The toxins in the intestine may have been destroyed by the permanganate, but the active vibrios in the gall-bladder would not be influenced by the drug and probably produced the second fatal collapse.

This condition of inflammation of the gall-bladder with a pure culture of the cholera vibrio in the bile is one of very considerable importance, as it may explain some of the severe toxic complications met with in cholera after the acute collapse stage has been recovered

from. As the toxin centre in the gall-bladder will not be affected by drugs, such as permanganate, given by the mouth with the object of destroying the toxin of cholera in the intestine, further research on the problem of killing the cholera vibrio in the tissue of the human host is required. The recent advances in chemo-therapy of Ehrlich, Morgenroth, and others, encourage the hope that it may be possible to obtain a chemical substance capable of destroying the cholera vibrio without damaging the tissues of the host too severely. If such a drug were obtained, it would be undoubtedly of enormous help in preventing the spread of cholera. Perhaps in the meantime serum or vaccine therapy may afford a means of dealing with the vibrios in the tissues.

The occurrence of the comma bacilli in the consolidated area of a lung in one of the cases in which the gall-bladder was intensely inflamed and the bile contained a pure culture of the cholera vibrio, was interesting and suggestive. It must have gained access to this point *viâ* the blood stream. From the point of view of prevention of cholera, the occurrence of the cholera vibrio in the consolidated area of the lung is of importance because it may gain an exit in the sputum to the external world and the possibility of this occurrence must be remembered in disinfecting the discharges of the patient.

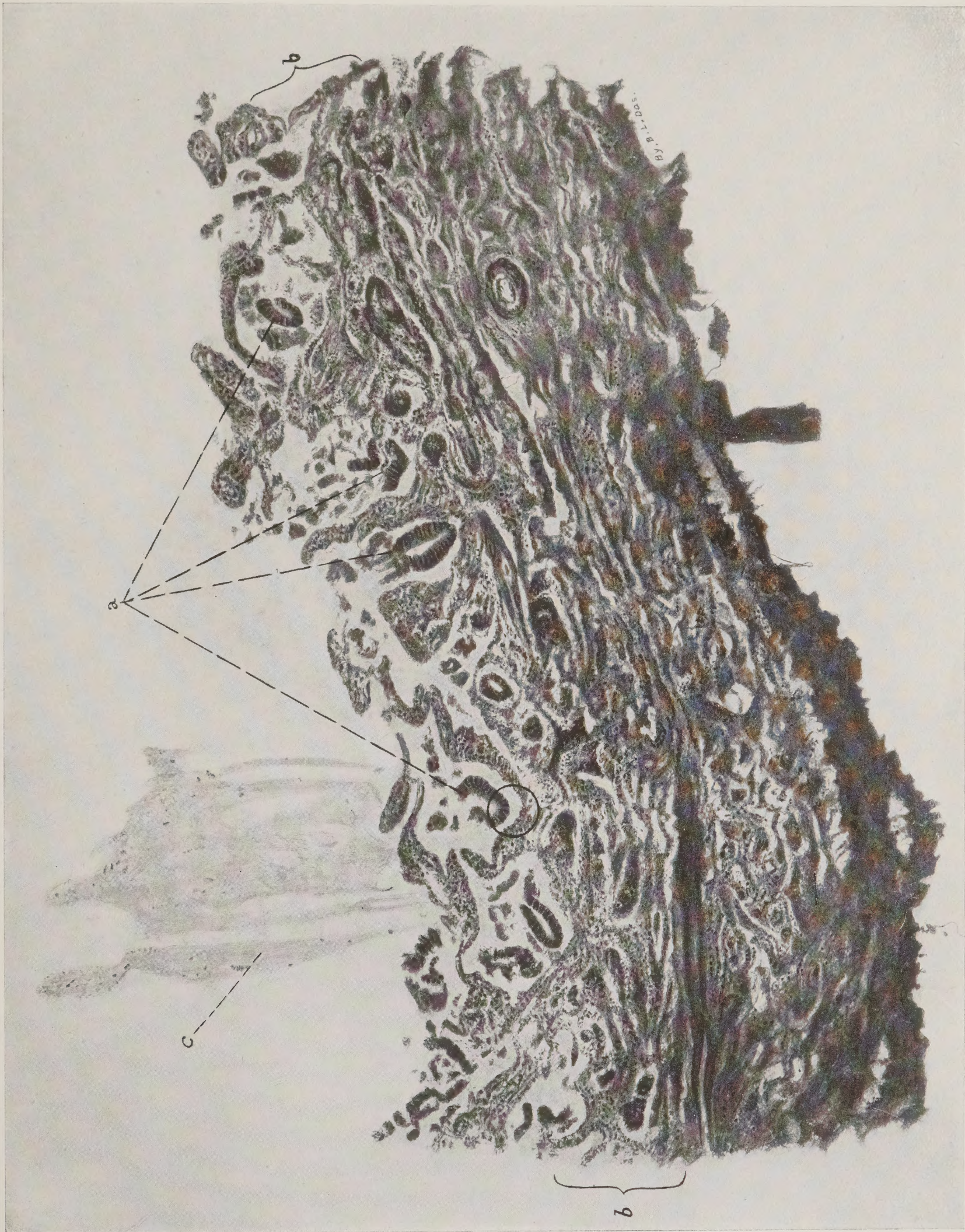
I am at present making a histological investigation of all the gall-bladders taken from cholera cases which showed naked eye pathological changes. I hope to publish with drawings the results of this study later.

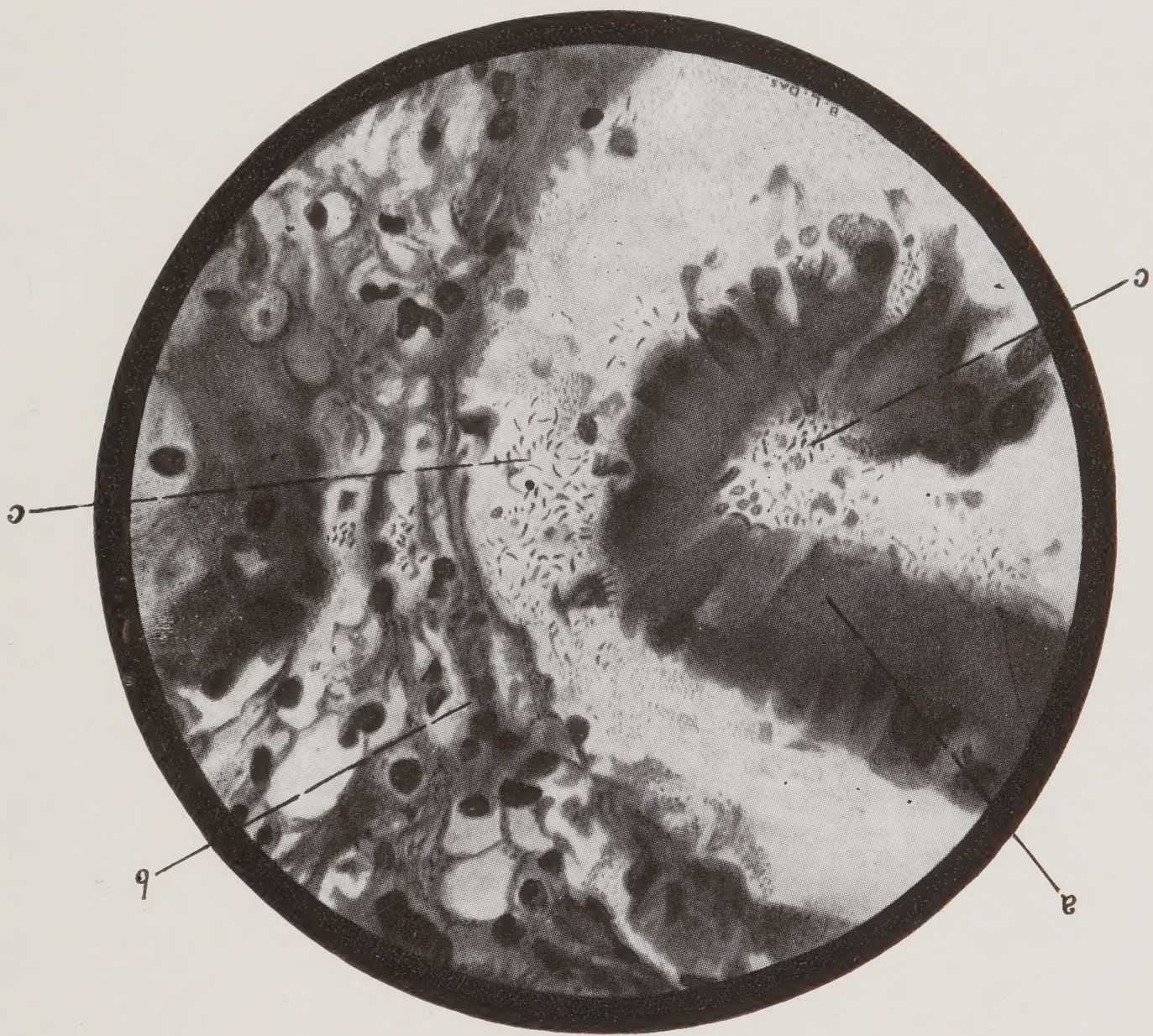
Description of drawings.—I have had drawings made to show the appearance of the gall-bladder wall on section of case No. 154. (Plate X.) The gall-bladder of this case showed naked eye pathological changes, and the bile contained a pure culture of the cholera vibrio.

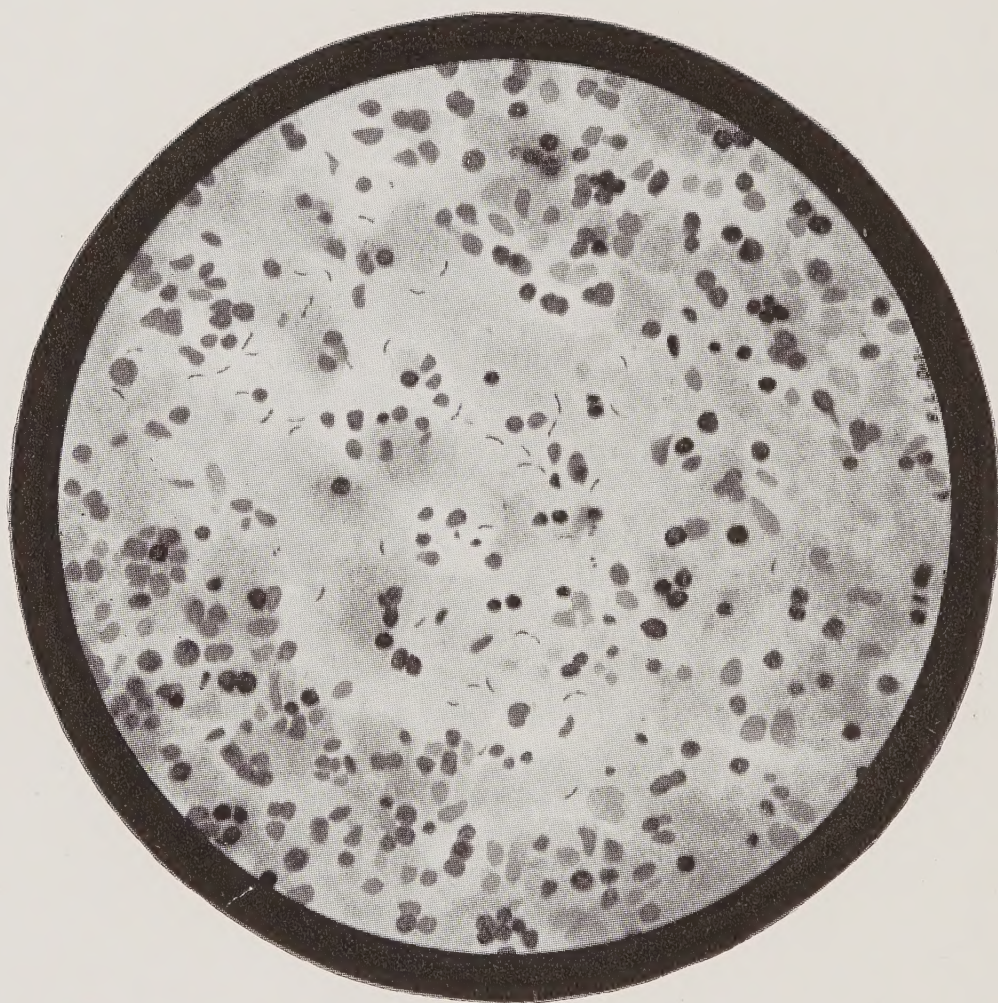
Two drawings have been made :—(Plates X and XI.)

(1) *Low power.*—This shows the general appearance of the wall on section. The mucous membrane is seen to have been cast off and only stumps of the epithelial layer remain. In the submucous layer there is a considerable cellular increase. At one point in the drawing a stained granular band of mucus is seen ; this, as will be seen in the high power drawing, contains cholera vibrios.

(2) *High power (oil immersion 1-12th).*—This shows a large number of cholera vibrios ; they are seen on the surface of an epithelial







stump and also underneath it, and they also extend into the submucous layer. From this it will be evident that the comma bacilli are present not only on the surface but extend into the submucous layers.

I have also had a drawing made of a section of a consolidated portion of the lung of case No. 269, Plate XII. The gall-bladder was intensely inflamed and the bile contained a pure culture of the cholera vibrio. The patient recovered from the acute attack of cholera but died 12 days later of uræmia and pneumonia. The case has been fully described by me.²⁴

High power (oil immersion 1-12th) Section of consolidated area of lung, Plate XII.—This shows the cellular exudation filling an alveolus; amongst the cells a number of comma bacilli can be clearly seen. Some forms are in the process of disintegration, as shown by the beading.

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